BENHA MEDICAL JOURNAL bmj
Print ISSN 1110-208X.
Online ISSN 2357-0016

Original article

Role of Splenic and Hepatic Stiffness Measurements in Determining the Degree of Thrombocytopenia in Patients with Liver Cirrhosis

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Received:23 April 2022

Accepted:25 March 2025

Abstract:

Background: The etiology of liver cirrhosis (LC) varies widely with many causes and fibrosis is the precursor of cirrhosis. Thrombocytopenia is common in advanced liver disease, as well as splenomegaly. The degree of liver and spleen stiffness can be assessed noninvasively by liver stiffness measurements (LSM) called transient elastography (TE). **Aim:** to evaluate the relationship between spleen, liver stiffness measured by TE and the degree of thrombocytopenia in patients with LC. **Methods:** this study included 50 patients suffering from compensated liver cirrhosis and has thrombocytopenia. All studied patients were subjected to complete history taking physical examination, liver tests, complete blood count and random blood sugar, sonography, and transient elastography of the liver and spleen. Thrombocytopenia was categorized as mild (platelets count 75,000-150,000/µL), moderate (50, 000-75,000/ µL) and severe (<50,000/ µL). **Results:** Mean (±SD) liver stiffness was 31.8±10.3 kPa, mean (±SD) splenic stiffness was 59.6±13.5 kPa. Fibro liver was significantly higher in moderate, severe, moderate severe thrombocytopenic cases ($p<0.001$, $=0.003$, <0.001 respectively). Receiver operating characteristic curve (ROC) was conducted for discrimination between cirrhotic patients with mild versus moderate or severe thrombocytopenia. High accuracy AUC was found (AUC=0.924, 0.972 respectively). Regarding fibroliver, at best cut off value (=38.7 kPa), sensitivity was 87.5%, specificity was 88.1%, PPV was 58.3%, NPV was 97.4%% and accuracy was 88%. Regarding fibrospleen, at best cut off value (=73 kPa), sensitivity was 100%, specificity was 92.9%, PPV was 72.8%, NPV was 100%% and accuracy was 94%. Fibroliver showed significant positive correlations with total, direct bilirubin, INR ($rs>0$; $p<0.001$ for each), significant negative correlations with albumin and PT ($rs<0$, $p<0.001$, $=0.015$ respectively). Otherwise, no significant correlations were found regarding of liver stiffness with other parameters among studied cases ($p>0.05$ for each). **Conclusion:** The degree of thrombocytopenia was directly correlated with liver and spleen stiffness values in cirrhotic patients.

Keywords: Liver cirrhosis, Liver Stiffness, Splenic Stiffness, Thrombocytopenia, Transient elastography.

Introduction

Liver cirrhosis is a late stage of fibrosis of the liver, fibrosis is a wound-healing response that occurs due to chronic liver injury [(1)]. Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis and characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, causing distortion of hepatic vascular architecture [(2)]. Liver fibrosis is due to various factors, such as alcohol consumption, non-alcoholic steatohepatitis (NASH), viral hepatitis, autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), and cholestatic liver diseases [(3)]. These result in generation of a chronic inflammation and accumulation of extracellular matrix (ECM) components, leading to fibrous scar formation [(4)].

Thrombocytopenia is defined as platelet count that falls below 150,000/microliter (for adults). Platelets are helping in blood clotting and wound healing [(5)]. Thrombocytopenia often discovered incidentally [(6)]. Thrombocytopenia is one of the most common and first hematological abnormalities seen in patients with chronic liver disease (CLD) [(7,8)]. It approximately affects 6% of patients without cirrhosis and 70% of patients with cirrhosis. Thrombocytopenia can often be used as a marker of advanced liver disease, and strong independent predictor of mortality [(9)].

TE is better at the identification of liver cirrhosis compared with significant fibrosis (mean AUROC 94% vs. 84%, respectively), and among hepatitis patients, it is better at excluding than confirming liver cirrhosis (negative predictive value 96%, positive predictive value 74%) [(10)]. TE is the non-invasive standard for the measurement of liver stiffness, and it is the most accurate non-invasive method for the identification of liver cirrhosis in patients with chronic viral hepatitis [(11)].

The aim of this study was to evaluate the relationship between spleen, liver stiffness measured by TE and the degree of thrombocytopenia in patients with LC.

Patients and methods

This study is a cross-sectional study, carried out on 50 patients suffering from compensated liver cirrhosis and has thrombocytopenia, they presented to the Internal Medicine Department of Benha University Hospital and National Liver Institute, Menoufia University in the period from June 2019 to September 2021. They were recruited from the out- or in-patients.

Written consent forms approved by local ethical research committee were obtained from every patient.

Inclusion Criteria:

- Age ≥18 years old.
- Compensated liver cirrhosis
- Thrombocytopenia.

Exclusion criteria:

- Previously underwent interferon therapy
- Taking drugs known to interfere with bone marrow function.
- Had moderate to severe ascites.
- Had hepatocellular carcinoma, portal vein thrombosis, or any space-occupying lesion in the liver.

All patients were adults, with mean age of 53.1 years. They were 36 males and 14 females, out of all studied cases, 26% had diabetes mellitus (DM). Patients were selected from the Internal Medicine Department of Benha University Hospital. Written consent forms approved by local

ethical research committee were obtained from every patient subject.

All studied patients underwent liver tests, complete blood count and random blood sugar level after taking complete history taking and physical examination. Thrombocytopenia was categorized as mild (platelets count 75,000-150,000/µL), moderate (50,000-75,000/ µL) and severe (<50,000/ µL) **(12)**.

The abdominal ultrasound (US) was performed after a minimum initial fasting period of 8 hours with B-mode US on grayscale, which was used to assess the liver and spleen dimensions, with a 3.75-MHz convex probe (SSA-700A; Toshiba Medical Systems Co, Ltd, Tokyo, Japan). Liver and spleen stiffness measurements were performed by transient elastography (FibroScan; Echosens, Paris, France) after at least 6 hours of fasting, using the elastography point quantification (ElastPQ) technique, During the procedure, the subjects were asked to pause breathing for a few seconds to minimize the hepatic movement occurring with respiration. All measurements were made at the end of the inspiration period. After traditional hepatic US images were obtained, the target area was determined, and the measurements were performed after positioning the range of imaging (ROI) on the target. All patients underwent single-day hematologic and biochemical testing, sonography, and transient elastography of the liver and spleen.

Liver biopsy is the gold standard for diagnosing cirrhosis as well as assessing the degree of inflammation (grade) and fibrosis (stage) of the disease. The diagnosis of cirrhosis by biopsy requires the presence of fibrosis and nodules. The nodular pattern can be micronodular, macronodular, or mixed with the micronodular pattern representing an independent risk factor for elevated hepatic venous pressure gradient (HVPG) and more severe disease **(13)**.

All patients were classified according to child Pugh score to assess the severity of liver cirrhosis. The Child-Pugh scoring system (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. Originally conceptualized by Child and Turcotte in 1964 to guide the selection of patients who would benefit from elective surgery for portal decompression, it broke down patients into three categories: A - good hepatic function, B - moderately impaired hepatic function, and C - advanced hepatic dysfunction. Their original scoring system used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status. The scoring system was modified later by Pugh et al., substituting prothrombin time for clinical nutrition status. Additionally, they introduced variable points for each criterion based on increasing severity **(14)**.

- Encephalopathy: None = 1 point, Grade 1 and 2 = 2 points, Grade 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, moderate = 3 points
- Bilirubin: under 2 mg/ml = 1 point, 2 to 3 mg/ml = 2 points, over 3 mg/ml = 3 points
- Albumin: greater than 3.5mg/ml = 1 point, 2.8 to 3.5mg/ml = 2 points, less than 2.8mg/ml = 3 points
- Prothrombin Time* (sec prolonged): less than 4 sec = 1 point, 4 to 6 sec = 2 points, over 6 sec = 3 points

*Frequently INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7 to 2.2 = 2 points, INR above 2.2 = 3 points

The severity of cirrhosis:

- Child-Pugh A: 5 to 6 points
- Child-Pugh B: 7 to 9 points
- Child-Pugh C: 10 to 15 points

Laboratory investigations including: -

The patients underwent liver tests

- ALT
- ALP
- GGT

- Bilirubin
- Albumin

Kidney functions tests

- urea
- Creatinine
- Estimated glomerular filtration rate (eGFR)

Statistical Analysis

The collected data was analyzed using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for windows, Version 25.0. Armonk, NY: IBM Corp.). Student T Test and Mann Whitney tests were used to assess the statistical significance of the difference between two study groups. For the comparison of more than two groups, one way analysis of variance (ANOVA) and Kruskal-Wallis test were used. Chi-Square test was used to examine the relationship between two qualitative variables. Correlation analysis: To assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. The optimum cut off point was defined as that which maximized the AUC value. Linear regression analysis was used for prediction of risk factors, using generalized linear models. A p value is considered significant if <0.05 at confidence interval 95%.

Results

All patients had mean age of 53.1 years. They were 36 males, out of all studied cases, 26% had diabetes mellitus. Laboratory investigations and patients characteristics are present in Table 1. Among all studied cases, 42 cases had mild thrombocytopenia (84%), 6 cases had moderate thrombocytopenia (12%) and 2 cases had severe thrombocytopenia (4%). Child score was assessed for all studied cases, 66% had class A5, 26% had class A6 and 8% had class B7. Splenomegaly was significantly associated with moderate, severe, moderate+severe thrombocytopenia when compared to mild thrombocytopenia (p=0.034, 0.049, 0.018 respectively). Fibroliver was significantly higher in moderate, severe, moderate+severe thrombocytopenic cases when compared to mild thrombocytopenic cases (p<0.001, =0.003, <0.001 respectively). Fibrospleen was significantly higher in moderate, severe, moderate+severe thrombocytopenic cases when compared to mild thrombocytopenic cases (p=0.001, =0.038, <0.001 respectively) (Table 2).

Fibroliver and fibrospleen were significantly higher in cases with splenomegaly when compared with those with no splenomegaly (p<0001 for each). (Table 3)

Receiver operating characteristic curve (ROC) was conducted for discrimination between cirrhotic patients with mild versus moderate or severe thrombocytopenia. High accuracy AUC was found (AUC=0.924, 0.972 respectively). Regarding fibroliver, at best cut off value (=38.7 kPa), sensitivity was 87.5%, specificity was 88.1%, PPV was 58.3%, NPV was 97.4%% and accuracy was 88%. Regarding fibrospleen, at best cut off value (=73 kPa), sensitivity was 100%, specificity was 92.9%, PPV was 72.8%, NPV was 100%% and accuracy was 94% (Figure 1).

Fibroliver showed significant positive correlations with total, direct bilirubin, INR (rs>0; p<0.001 for each), significant negative correlations with albumin and PT (rs<0, p<0.001, =0.015 respectively). Otherwise, no significant correlations were found regarding of liver stiffness with other parameters among studied cases (p>0.05 for each). (Table 4 & figure 1)

Table (1):- Labortaory investigations and patients' characteristics.

			Cases N=50
Total Bilirubin (mg/dL)		mean±SD	1±0.3
Direct Bilirubin (mg/dL)		mean±SD	0.4±0.1
Albumin (g//dL)		mean±SD	3.8±0.5
AST (U/L)		mean±SD	62.2±20.9
ALT (U/L)		mean±SD	53.2±15.9
PT (seconds)		mean±SD	83.9±11.3
INR		mean±SD	1.2±0.1
AFP (ng/mL)		median, range	7 (1-56)
Creatinine (mg/dL)		mean±SD	0.8±0.1
Hb (g/dL)		mean±SD	11.4±1.1
WBCs ($X10^9$/L)		mean±SD	5.7±1.3
Platelets ($X10^9$/L)		mean±SD	100.6±26.9
Fibro stages (4^{th} stage)		N (%)	**50 (100%)**
Splenomegaly		N (%)	**31 (62%)**
Liver stiffness		mean±SD	31.8±10.3
Splenic stiffness		mean±SD	59.6±13.5
thrombocytopenia grades	**Mild**	N (%)	42 (84%)
	Moderate	N (%)	6 (12%)
	Severe	N (%)	2 (4%)

AST: Aspartate Transferase; INR: International normalized ratio; ALT: alanine aminotransferase; PT: prothrombin time; AFP: Alpha-Fetoprotein; HB: Hemoglobin; WBCs: White blood cells.

Table (2):- Comparison of SM, FL, FS according to thrombocytopenia grades among studied cases.

		Thrombocytopenia								
		Mild	**Moderate**	**Severe**	**moderate+ severe**	p^1	p^2	p^3	p^4	p^5
		n=42	**n=6**	**n=2**	**n=8**					
Splenomegaly	**N (%)**	23(54.8%)	6 (100%)	2(100%)	8 (100%)	0.030	0.034	0.049	-	0.018
fibro liver	**mean±SD**	28.9±8.9	46.3±12	49.9±0.2	47.2±10.3	<0.001	<0.001	0.003	0.641	<0.001
fibro spleen	**mean±SD**	56.7±12.7	74.8±0.4	75±0	74.9±0.4	0.001	0.001	0.038	0.986	<0.001

P1, comparison between mild, moderate, severe; p2, comparison between mild and moderate; p3, comparison between mild and severe; p4, comparison between moderate and severe; p5, comparison between moderate +severe versus mild thrombocytopenia; p5, comparison between moderate +severe versus mild thrombocytopenia.

Table (3):- Comparison of Liver and Spleen Stiffness according to splenomegaly among studied cases.

	No splenomegaly N=19 mean±SD	**Splenomegaly N=31 mean±SD**	*P*
Fibro liver	24.5±6.8	36.3±11.2	<0.001
Fibro spleen	45.8±8.2	68±7.8	<0.001

Table (4). Validity of liver and spleen stiffness discrimination between cirrhotic patients with mild versus moderate or severe thrombocytopenia.

	fibro liver	**fibro spleen**
AUC	0.924	0.972
Cut off	38.7	73
Sensitivity (%)	87.5%	100%
Specificity (%)	88.1%	92.9%
PPV (%)	58.3%	72.8%
NPV (%)	97.4%	100%
Accuracy (%)	88%	94%

AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value.

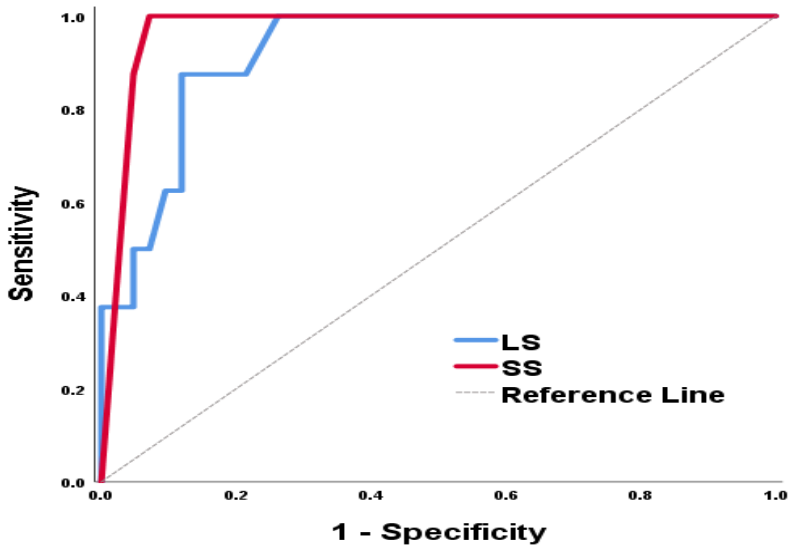

Figure (1):- ROC of liver and spleen stiffness discrimination between cirrhotic patients with mild versus moderate or severe.

Regression analysis was conducted for prediction of thrombocytopenia severity using age, gender, DM, AST, INR, Child score, SM, fibroliver and fibrospleen as covariates. Higher child score, fibroliver and fibrospleen levels were associated with risk of higher thrombocytopenia severity in univariable analysis. However, in multivariable analysis, only higher fibroliver and fibrospleen were considered independent predictors of more thrombocytopenia severity (table 5)

Fibroliver showed significant positive correlations with total, direct bilirubin, INR (rs>0; p<0.001 for each), significant negative correlations with albumin and PT (rs<0, p<0.001, =0.015 respectively). Otherwise, no significant correlations were found regarding of liver stiffness with other parameters among studied cases (p>0.05 for each). Fibrospleen showed significant positive correlations with total, direct bilirubin, INR (rs>0; p<0.001 for each), significant negative correlations with albumin and PT (rs<0, p<0.001, =0.045 respectively). Otherwise, no significant correlations were found regarding of fibrospleen with other parameters among studied cases (p>0.05 for each). (Table 6)

Table (5). Linear regression analysis for prediction of severity of thrombocytopenia.

	Univariable		Multivariable	
	B	***p***	***B***	***p***
Age	0.8	0.2		
Gender	2.3	0.8		
DM	2.5	0.8		
AST	-0.3	0.1		
INR	2.6	0.2		
Child Pugh score	1.3	**0.016**	3.5	0.193
fibroliver	-1.9	**<0.001**	-2.1	**<0.001**
fibrospleen	-2.2	**<0.001**	-2.5	**<0.001**

B, regression coefficient. DM: diabetes mellitus, AST: Aspartate Transferase; INR: International normalized ratio;

Table (6). Correlation of liver stiffness with other parameters among studied cases.

	fibroliver		fibrospleen	
	rs	***p***	***rs***	***p***
Age	-0.169	0.241	-0.183	0.203
Total Bilirubin	0.654	**<0.001**	0.805	**<0.001**
Direct Bilirubin	0.559	**<0.001**	0.737	**<0.001**
Albumin	-0.695	**<0.001**	-0.935	**<0.001**
AST	0.148	0.305	0.222	0.121
ALT	0.169	0.241	0.196	0.172
PT	-0.273	**0.015**	-0.267	**0.045**
INR	0.698	**<0.001**	0.883	**<0.001**
AFP	0.138	0.339	0.002	0.986
Creatinine	0.109	0.451	-0.123	0.395
HB	-0.245	0.086	-0.208	0.147
WBCs	-0.153	0.287	-0.198	0.168

rs, Spearman's correlation coefficient. AST: Aspartate Transferase; INR: International normalized ratio; ALT: alanine aminotransferase; PT: prothrombin time; AFP: Alpha-Fetoprotein; HB: Hemoglobin; WBCs: White blood cells.

Discussion

Liver cirrhosis is widely prevalent worldwide due to different causes **(15).** One of the main complications of liver cirrhosis is thrombocytopenia that can be associated with significant morbidity **(16).** Liver and spleen stiffness (LS and SS) can serve as a supplemental noninvasive assessment tool for detecting clinically significant portal hypertension **(17).** Elastography is widely used to assess LS and SS **(18).** In the present study, there were no significant association was found regarding age with thrombocytopenia grades among studied cases. While Yoshida et al found that platelet count decreased with age [19]. We found no significant association regarding gender, and DM with thrombocytopenia grades and this was in line with previous studies [19]. There were no significant association regarding bilirubin, albumin, AST, ALT, PT, INR, AFP, creatinine, Hb and TLC according to thrombocytopenia grades. While other study revealed that serum bilirubin levels and other liver function tests, was shown to increase as platelet count decreased [20]. Also, other researchers found a positive correlation between serum thrombopoietin and albumin levels [21]> While another study [22] found that, albumin levels significantly correlated with thrombocytopenia. While in a study done 2016 [23], it was found that, the degree of thrombocytopenia appears to be proportionally related to the severity of liver disease. In the present study, splenomegaly was significantly associated with moderate and severe thrombocytopenia which agreed with other reports [24,25]. On the other hand, a study has revealed that, there was no significant correlation between spleen size and peripheral platelet count in cases with decompensated liver cirrhosis [26]. In addition, our study showed that platelets count had significant negative correlations with total, direct bilirubin, INR, and significant positive correlations with albumin and PT. This agreed with other studies [19, 11]. While we did not notice an association between platelet count with ALT and AST, in agreement with other studies [19], although ALT and AST increased in most CLDs [27]. Assessment of LS in our study revealed significant correlation with the degree of thrombocytopenia, as noticed by other studies that revealed increasing LS with severe thrombocytopenia [28 ,29]. LS values combined with platelet counts are useful to rule out varices requiring treatment [30]. LS and platelet count should be assessed at regular intervals to reevaluate if an upper gastrointestinal endoscopy would be indicated [31]. We have demonstrated that LS showed significant positive correlations with total, direct bilirubin. In agreement with others who showed positive correlation between LS with bilirubin [32 & 33]. On the other hand, no significant relation was found between LS and bilirubin in other studies [34]. The current study showed that LS showed no significant correlations with AST and ALT. but in disagreement with those who found significant relation between LS versus AST and ALT [30]. While others found a positive correlation between ALT levels and LS at the onset of acute viral hepatitis [35,36]. The current study demonstrated that LS showed significant positive correlations with INR, and significant negative correlations with albumin and PT, as found by others who reported that there were strong association between LS and serum albumin and PT [37 ,38]. And by comparing LS with the splenic size, we revealed that fibro liver was significantly higher in cases with splenomegaly when compared with those with no splenomegaly. These results agreed with other studies [25,39] SS was significantly correlated with degree of thrombocytopenia in the present study, in agreement with others [25]. Moreover, the SS was significantly higher in our cases with splenomegaly when compared with those with no splenomegaly, in consistent with others who reported that SS was significantly correlated with the

splenomegaly [25, 40]. On the other hand, other reported that there was no association between SS and spleen size [41]. Other study again has found that SS showed a higher correlation with both splenic diameter and splenic area [42]. SS in the current study had significant positive correlations with total, direct bilirubin, INR, and significant negative correlations with albumin and PT. These results agreed with others [43, 44]. Both LS and SS had excellent discrimination between grades of thrombocytopenia, although SS was superior to LS (AUC=0.972, 0.924 respectively). Moreover, SS and LS were considered as independent predictors for more severe thrombocytopenia in our results, although SS was superior to LS. In agreement with other studies which showed that although LS was significantly correlated with the platelet count, SS had a better correlation with different degrees of thrombocytopenia **[25]**. Ma and colleagues reported that SS was superior to LS in predicting esophageal varices in patients with chronic liver diseases **[45]**. SS rises principally by splenic congestion, which eventually leads to parenchymal fibrosis by architectural changes and blood retention in splenic arteries and veins **[56]**. So SS has a stronger correlation with both platelet count and splenomegaly if compared to LS and this is further implies the very likely association between SS and the pathophysiology of portal hypertension **[45].** It has been reported that reproducibility of SS measurement by elastography depends on operator's expertise and that education is critical **[46]**. In the present study, SS and LS measurements were performed by the same radiologist to eliminate the operator bias. SS measurement using elastography was affected by other confounders such as BMI, spleen size, interposition of the lung between the abdominal wall and the spleen blocked the US window as well as the abdominal wall thickness **[47]**. Care should be taken when comparing measurements between elastography techniques as differing parameters are reported [48]. Several clinical studies indicated that the platelet count can distinguish significant fibrosis in patients with liver cirrhosis and may be used to assess the degree of liver steatosis and fibrosis**.** Higher histologic fibrosis scores were significantly associated with decreased platelet counts **[49]** The main limitation of this study was the small number of patients available for analysis, especially in the group with severe thrombocytopenia.

Conclusion:

Compared to LS, SS shows a better significant correlation with the platelet count and spleen size in patients with cirrhosis. The degree of thrombocytopenia was directly correlated with SS values in cirrhotic patients, irrespective of the presence of splenomegaly.

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To cite this article: Sherif I. Negm, Eman Abdelsameea , Medhat A.khalif , Ghada G. Gadallah . Role of Splenic and Hepatic Stiffness Measurements in Determining the Degree of Thrombocytopenia in Patients with Liver cirrhosis. BMFJ 2025;42(4):663-673.